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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/535 — A1

(11) International Publication Number: **WO 99/58130**

(43) International Publication Date: 18 November 1999 (18.11.99)

(21) International Application Number: PCT/US99/06523

(22) International Filing Date: 14 April 1999 (14.04.99)

(30) Priority Data:
60/084,860 8 May 1998 (08.05.98) US

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NEW DRUG COMBINATIONS OF A N.A.R.I., PREFERABLY REBOXETINE, AND PINDOLOL

(57) Abstract

This patent application describes a new combination treatment of selective, noradrenaline–reuptake inhibitors (NARI) and specifically, reboxetine, and pindolol to provide rapid relief to patients suffering from depression, general anxiety, attention deficit hyperactivity disorder (ADHD), anxiety disorders such as obsessive compulsive disorders (OCD), panic disorders (PD), social phobia (SD) and the like.

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NEW DRUG COMBINATIONS OF A N.A.R.I., PREFERABLY REBOXETINE, AND PINDOLOL

Field of the Invention

This invention describes new treatments that should provide for a fast acting rapid onset of relief from several nervous system disorders, and it involves the administration of the drug reboxetine in combination with the drug pindolol.

Background

The introduction of tricyclic antidepressants in the early 1960s has provided a major advance in the treatment of neuropsychiatric disorders. Reactive and endogenous depressions, diagnoses formerly carrying grave prognostic implications, have become, with the introduction of the tricyclics, manageable disorders with a much smaller toll on the patient and the society as a whole.

The early tricyclic compounds were reuptake inhibitors of all the catecholamines released in the synaptic cleft, thus resulting in prolongation and enhancement of the dopamine (DA), noradrenaline (NA) and serotonin (5-hydroxytryptamine = 5-HT) action. Lack of selectivity also causes undesired side effects particularly on the acetylcholine (especially the muscarinic component), and histamine mediated neurotransmission.

Because of these unwanted pharmacodynamic activities, cognitive impairment, sedation, urinary and gastrointestinal tract disturbances, increased intraocular pressure were limiting factors in the clinical use of these compounds and often required discontinuation of treatment. Of utmost concern were also the cardiac toxic effects and the proconvulsant activity of this group of drugs.

More recently, selective reuptake inhibitors for serotonin (SSRI) have been introduced with definite advantages in regard to fewer side effects without loss of efficacy.

Summary of the Invention

Here we present the surprising finding that when the drug pindolol is given to a patient concurrently with a drug from a new category of antidepressants, a so called noradrenaline (NA) reuptake inhibitor (NARI), the combination of drugs act with surprising speed in relieving the symptoms of depression and it may be used for treating the symptoms of other central nervous system disorders including, but not only, general anxiety, Addictive Disorders, attention deficit hyperactivity disorder (ADHD), anxiety disorders such as

obsessive compulsive disorders (OCD), panic disorders (PD), social phobia (SP) and the like.

One particular NARI that is preferred is reboxetine. Reboxetine is the generic name of the pharmaceutical substance with the chemical name of 2-(I-((2-ethoxyphenoxy)benzyl)-morpholine, and its pharmaceutically acceptable salts. Reboxetine can be a free base, or it can include reboxetine methanesulfonate (also called reboxetine mesylate) or any other pharmaceutically acceptable salt that does not significantly affect the pharmaceutical activity of the substance.

The chemical name of pindolol is 1-(1H-Indol-4-yloxy)-3-[(1-methylethyl)amino]-2-propanol; 4-[2-hydroxy-3-(isopropylamino)-propoxy]indole; pinodolol. Pindolol is described in US patent no. 3,471,515, incorporated by reference and process steps are described in Swiss patents 469,002 and 472,404, assigned to the Sandoz Company, now the Novartis company, all documents incorporated into this document by reference. It has the trade name VISKEN®.

The present invention provides for the dosing of both reboxetine and pindolol, concurrently. The dosages for reboxetine and pindolol can be measured separately. The two drugs can be given as a single combined dose or given separately. They may be given at the same or at different times as long as both drugs are in the patient at one time over a 24 hour period. The two drugs will preferably be given to the patient, concomitantly, concurrently, at or about the same time, within about 5, 10, or 30 minutes, or they may be given within 1, 2, 3, 4, 5, 6, 8, 10, 12, 18 or about 24 hours, or fractions of minutes or of hours of each other. Concomitant or concurrent administration means the patient takes one drug within about 5 minutes of taking the other drug. Because the goal here is to provide rapid symptomatic relief to the patient, in most cases when treatment is started the two drugs would be administered to the patient close in time and typically concomitantly; thereafter, the timing of each drug's administration may not be as important.

A preferred dose range of reboxetine is 4 to 10 mg per patient per day and the more preferred dose is 6 to 8 mg or 8 to 10 mg per patient daily, depending upon the patient, delivered twice a day (b.i.d.). The reboxetine should be given to a patient concurrently with pindolol.

A preferred dose range of pindolol is 10-60 mg per patient per day and the more preferred dose is about 10 mg per patient daily, depending upon the patient, delivered twice

a day (b.i.d.). Preferably the pindolol should be given concurrently with reboxetine as described above.

Additional Description of the Invention and Description of the Preferred Embodiment(s)

Reboxetine is the generic name of the pharmaceutical substance with the chemical name of 2-(I-((2-ethoxyphenoxy)benzyl)-morpholine, and its pharmaceutically acceptable salts. Reboxetine can be a free base, or it can include reboxetine methanesulfonate (also called reboxetine mesylate) or any other pharmaceutically acceptable salt that does not significantly affect the pharmaceutical activity of the substance. Reboxetine and a method of synthesis are described in U.S. 4,229,449, issued 21 Oct. 1980, Melloni et. al., incorporated by reference into this document, methods of preparation are described in US 5,068,433, issued 26 Nov. 1991, Melloni et. al. and in US 5,391,735, issued 21 Feb. 1995, both incorporated by reference. Reboxetine may also be known under the trade name of EDRONAX™.

The pharmaceutical compositions and methods of administration described in US 4,229,449 at col. 18, lines 33-66 are specifically incorporated by reference. Twice a day dosing is preferred with current formulations.

Reboxetine acts as an antidepressant. Antidepressants are frequently grouped into categories or "generations." The first generation of antidepressants were usually tricyclic antidepressants such as maprotiline that affected various neurotransmitter systems and are associated with many undesirable side effects. The second generation of antidepressants, such as mianserine, mirtrazapine and trazodone are largely devoid of anticholinergic action and their adrenolytic and antihistaminic effects are weaker. These are contrasted with the third generation of antidepressants (e.g. SSRI, ipsapirone, viloxazine, reboxetine, bupropione) that mediate only one of the three main neurotransmitter system for depression (5-HT, noradrenaline, dopamine) and they do not affect muscarine, histamine and adrenergic cerebral systems. Svestka, J. "Antidepressives of the 3rd, 4th and 5th generation," Cesk-Psychiatr. 1994 Feb; 90(1):3-19. (Czech).

Reboxetine, however, does not act like most antidepressants. Unlike tricyclic antidepressants and even selective serotonin reuptake inhibitors (SSRIs), reboxetine is ineffective in the 8-OH-DPAT hypothermia test, indicating that reboxetine is not a selective

serotonin reuptake inhibitor rather it is selective for the noradrenergic system. Thus, reboxetine is not an SSRI, rather it is considered a novel, selective, noradrenaline-reuptake inhibitor (NARI). Leonard-BE, "Noradrenaline in basic models of depression." *European-Neuropsychopharmacol.* 1997 Apr; 7 Suppl 1: S11-6; discussion S71-3. Unlike most drugs, reboxetine is a highly selective norepinephrine uptake inhibitor, with only marginal serotonin and no dopamine uptake inhibitory activity. The compound displays only weak or no anti-cholinergic activity in different animal models and is devoid of monoamine oxidase (MAO) inhibitory activity.

Reboxetine is highly potent and fast acting. Our investigations indicate reboxetine has potent antireserpine activity and combines the inhibitory properties of classical tricyclic antidepressants on the reuptake of noradrenaline with an ability to desensitize β-adrenergic receptor function without showing any appreciable interaction with muscarinic cholinergic and I-adrenerigic receptors. Moreover, reboxetine shows less vagolytic activity than other tricyclic antidepressants.

In spite of the inherently fast action of reboxetine there is still a "lag" or delay from the time of administration of the drug until the time the drug provides symptomatic relief to the patient. The treatments described here decrease that lag time. A period of days and especially weeks between the administration of a drug and its effect in relieving depression can be devastating to a patient. The patient may conclude the drug is not effective and stop taking the drug, thus a quick onset of activity is critically important for treatments of this type. We have discovered that the combination of pinodolol and reboxetine provides highly effective relief of psychiatric disorders with a minimal delay in onset of activity.

Pindolol is the generic name for 1-(1H-Indol-4-yloxy)-3-[(1-methylethyl)amino]-2-propanol; 4-[2-hydroxy-3-(isopropylamino)-propoxy]indole; prinodolol. Pindolol is described in US patent no. 3,471,515, incorporated by reference and process steps are described in Swiss patents 469,002 and 472,404, assigned to the Sandoz Company, now the Novartis company, all documents incorporated into this document by reference. It has the trade name VISKEN®.

The dosage used to treat all of the disorders described here may be found above and below. Reboxetine is well tolerated and has a wide safety range, it can be administered in a dose range of active ingredient from about 1 to over 40 mg/kg. It is more commonly provided in dosages of from 1 to 20 mg per patient per day. Pindolol is also fairly safe although it is contraindicated for patients with bronchial asthmas, cardiac failure, heart block

and severe bradycardia. Other adverse reactions are possible. Pindolol dosages in the range of 5 to 60 mg daily can be effective. Both compounds may be administered by any suitable method including a convenient oral dosage form. A preferred method is oral dosing twice a day. The preferred dose range of reboxetine is 4 to 20 and more preferably 4 to 10 mg per patient per day and the preferred dose range of pindolol is 10 - 20 mg per patient per day. When starting medication the more preferred dose of reboxetine is 6 to 8 mg or 8 to 10 mg and pindolol is 10 mg per patient daily, depending upon the patient, delivered twice a day (b.i.d.). It can also be given at dosages of 2, 4, 6, 8, 10 or 12 mg/patient per day or fractions thereof: For example, suitable administrations could be 4 mg of reboxetine and 5 mg of pindolol in the morning and 2 or 4 mg of Rebozetine and 5 mg of pindolol in the evening. A skilled practitioner would be expected to determine the precise level of dosing. The idea dosing would be routinely determined by an evaluation of the patient and the needs of the patient.

This patent application describes the treatment of numerous conditions, disorders, diseases, and disease symptoms with the combination of drugs described herein, in addition to the conditions, disorders, diseases, and disease symptoms described above, the following may also be treated with these drugs: Addictive Disorders, Psychoactive Substance Use Disorders, Nicotine Addition or Tobacco Addiction (with a result of Smoking Cessation or a decrease in smoking) and Attention Deficit Hyperactivity Disorder (ADHD). This patent application also describes the treatment of Obsessive Compulsive Disorders (OCD), and Panic Disorder (PD), comprising administering a therapeutically effective, nontoxic dose of the drugs described herein and derivatives and or pharmaceutically acceptable salts thereof to a patient

Addictive Disorders and Psychoactive Substance Use Disorders, such as Intoxication disorders, Inhalation disorders, Alcohol addiction, Tobacco Addiction and or Nicotine Addiction. Tobacco and Nicotine addiction would be treated with the goal of achieving either Smoking Cessation or Smoking Reductions.

Addictive Disorders, Alcohol and Other Psychoactive Substance Use Disorders, disorders related to Intoxication and Inhalants and especially Tobacco Addiction or Nicotine Addiction, may be treated with the drugs described herein. Tobacco Addiction or Nicotine Addiction would be treated with the drugs described herein in order to achieve smoking/chewing cessation or smoking/chewing reduction. General descriptions of

Addictive Disorders, including disorders related to Intoxication and Inhalants and Tobacco Addiction or Nicotine Addiction may be found in many standard sources, such as, The American Psychiatric Press Textbook of Psychiatry, Second Edition, Edited by Robert E. Hales, Stuart C. Yudofsky, and John A. Talbott, copyright 1994, incorporated by reference, especially pp. 401 et. seq., section on "Nicotine" incorporated by reference. Another of many texts is the Manual of Psychiatric Therapeutics, Second Edition, edited by Richard I. Shader, incorporated by reference, especially pp. 85 from Chapter 11 (Hypnosis).

The treatment of Alcohol and Other Psychoactive Substance Use Disorders, such as disorders related to Intoxication and Inhalants and Tobacco Addiction or Nicotine Addiction but especially Tobacco Addiction involves the administration of the drugs described herein in a manner and form that provide a reduction in the symptoms of the disease. Tobacco Addiction or Nicotine Addiction in particular would be treated to achieve a reduction or cessation of smoking or chewing of nicotine containing materials by a patient. Cessation or a reduction in smoking or chewing of addictive or psychoactive substances involves the administration of the drugs described herein in a manner and form that provide a reduction in the symptoms of the disease, or with Tobacco or Nicotine with a reduction in the amount smoked or chewed.. See the general description above for administration of Reboxetine.

Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is a condition or disease state that may be treated with the drugs described herein. General descriptions of ADHD, may be found in many standard sources, such as, The American Psychiatric Press Textbook of Psychiatry, Second Edition, Edited by Robert E. Hales, Stuart C. Yudofsky, and John A. Talbott, copyright 1994, incorporated by reference, especially pp. 741 et. al., section on "ADHD," incorporated by reference. Another of many texts is the Manual of Psychiatric Therapeutics, Second Edition, edited by Richard I. Shader, incorporated by reference, especially Chapter 18, Attention-Deficit hyperactivity Disorder, and pp. 172 et. seq., incorporated by reference.

The treatment of Attention Deficit Hyperactivity Disorder in children and adults involves the administration of the drugs described herein in a manner and form that provide a reduction in the symptoms of the disease. A child or young adult may require a smaller dosage depending upon the size, age, condition of the patient. See general description above for administration of the drugs described herein.

Obsessive Compulsive Disorders (OCD)

Obsessive Compulsive Disorder is a condition or state of anxiety that may be treated with reboxetine. General descriptions of OCD, may be found in many standard sources, such as, The American Psychiatric Press Textbook of Psychiatry, Second Edition, Edited by Robert E. Hales, Stuart C. Yudofsky, and John A. Talbott, copyright 1994, incorporated by reference, especially the chapter on "Anxiety Disorders," incorporated by reference. Another of many texts is the Manual of Psychiatric Therapeutics, Second Edition, edited by Richard I. Shader, incorporated by reference, especially Chapter 5, Obsessions and Compulsions, more particularly, Section III of that chapter, "OCD" pp. 36 *et. seq.*, incorporated by reference.

The treatment of Obsessive Compulsive Disorders (OCD) involves the administration of reboxetine in a manner and form that provide a reduction in the symptoms of the disease. See general description above for administration of reboxetine.

The following study shows the therapeutic effectiveness of using reboxetine in doses varying from 6 to 8 mg to treat OCD. This study is provided to illustrate the usefulness of using reboxetine as a treatment for OCD and the invention described herein should not be considered limited by this example.

In a trial involving 10 patients with a DSM-III-R diagnosis of Obsessive Compulsive Disorder who were all treated with reboxetine for a period of 3 to 4 weeks with the dose for the first week at 6 mg (4 mg in a.m. and 2 mg in p.m.) with the dose increasing in the second week to 8 mg (4 mg b.i.d.). At CGI last assessment, one patient was judged very much improved, 4 were judged much improved, 2 minimally improved, while 3 were unchanged. Of the patients who did respond they had a decrease of the obsessive-compulsive symptomatology, as measured by the CPRS-OC rating scale, of more than 30 and as much as 73%.

Panic Disorder (PD)

Panic Disorder is a condition or state of anxiety that may be treated with reboxetine. General descriptions of PD, may be found in many standard sources, such as, The American Psychiatric Press Textbook of Psychiatry, Second Edition, Edited by Robert E. Hales, Stuart C. Yudofsky, and John A. Talbott, copyright 1994, incorporated by reference, especially the chapter on "Anxiety Disorders," incorporated by reference, another of many texts is the Manual of Psychiatric Therapeutics, Second Edition, edited by Richard I. Shader, incorporated by reference, especially Chapter 25, "Approaches to the Treatment of Anxiety States," incorporated by reference.

The treatment of Panic Disorder involves the administration of the drugs described herein in a manner and form that provide a reduction in the symptoms of the disease. See general description above.

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Claims

1. A single dosage form of reboxetine and pindolol.

2. The single dose of claim 1 where the form is a tablet, hard or soft capsule or caplet.

3. The single dose of claim 1 where the amount of reboxetine is 5 mg and the amount of pindolol is 7.5mg.

4. A method of treating a patient experiencing symptoms selected from; depression, general anxiety disorders (GADs), Addictive Disorders, attention deficit hyperactivity disorder (ADHD), and anxiety disorders such as obsessive compulsive disorder (OCD), panic disorder (PD), social phobia (SP), comprising the administration of a therapeutically effective, nontoxic dose of pindolol, its derivatives and or pharmaceutically acceptable salts thereof to a patient and administering a therapeutically effective, nontoxic dose of a selective, a noradrenaline reuptake inhibitor (NARI), its derivatives and or pharmaceutically acceptable salts thereof to a patient.

5. A method of treating a patient as in claim 4 where the noradrenaline reuptake inhibitor (NARI) is reboxetine.

6. A method of treating a patient as in claim 5 where the administration of the dose of pindolol is administered within 24 hours of the administration of the dose of reboxetine.

7. The method of claim 6 where the pindolol is administered within 12 hours of the reboxetine.

8. The method of claim 7 where the pindolol is administered within 6 hours of the reboxetine.

9. The method of claim 8 where the pindolol is administered within 3 hours of the reboxetine.

10. The method of claim 9 where the pindolol is administered within 1 hour of the reboxetine.

11. The method of claim 10 where the pindolol and reboxetine are administered concomitantly.

12. The method of claim 5 where the patient is experiencing symptoms of depression.

13. The method of claim 5 where the patient is experiencing symptoms of general anxiety disorders (GADs).

14. The method of claim 5 where the patient is experiencing symptoms of Addictive Disorders.

15. The method of claim 5 where the patient is experiencing symptoms of attention deficit hyperactivity disorder (ADHD).

16. The method of claim 5 where the patient is experiencing symptoms of obsessive compulsive disorder (OCD).

17. The method of claim 5 where the patient is experiencing symptoms of panic disorder (PD).

18. The method of claim 5 where the patient is experiencing symptoms of social phobia (SP).

19. The use of reboxetine and pindolol, their derivatives and or pharmaceutically acceptable salts thereof in the manufacture of a medicament comprising an effective, nontoxic dose of reboxetine and pindolol to treat general anxiety disorders (GADs), Addictive Disorders, attention deficit hyperactivity disorder (ADHD), and anxiety disorders such as obsessive compulsive disorder (OCD), panic disorder (PD), social phobia (SP), and/or for the treatment of any of the symptoms of those diseases.

20. The method or use in claims 1-19 where the reboxetine dose range is from about 4 to 10 mg. per patient per day and the pindolol dose range is from about 10 to 20 mg. per patient per day, delivered twice a day.

21. The method or use in claims 1-19 where the reboxetine dose range is from about 6 to 8 mg. per patient per day and the pindolol dose range is from about 10 to 16 mg. per patient per day, delivered twice a day.

INTERNATIONAL SEARCH REPORT

Im tional Application No
PCT/US 99/06523

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 687 472 A (LILLY CO ELI) 20 December 1995 (1995-12-20) page 2, line 28-32; claims 1,2,5,6,9,10,13-15 page 11, line 15-55 page 14, line 14-36 ---	1,4-12, 16,19
X	EP 0 759 299 A (LILLY CO ELI) 26 February 1997 (1997-02-26) page 12, line 57 - page 13, line 13; claims 1,2,4,5,7,9,13,14 --- -/--	1,2, 4-12,19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 August 1999	19/08/1999

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INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 99/06523

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	REDROBE ET AL: "The Role of 5-HT1A and 5-HT1B Receptors in Antidepressant Drug Actions in the Mouse Forced Swimming Test" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 318, no. 2/3, 30 December 1996 (1996-12-30), pages 213-220, XP002111616 page 214; figure 4 page 217, left-hand column, paragraph 3 - right-hand column, paragraph 1 ---	1,4-12, 19
X	BLIER ET AL: "Selective Activation of Postsynaptic 5-HT1A Receptors Induces Rapid Antidepressant Response" NEUROPSYCHOPHARMACOLOGY, vol. 16, no. 5, 1997, pages 333-338, XP002111617 page 333, left-hand column page 335-336 ---	1-21
A	MORENO ET AL: "Pindolol Augmentation of Treatment-Resistant Depressed Patients" JOURNAL OF CLINICAL PSYCHIATRY, vol. 58, no. 10, 1997, pages 437-439, XP002111618 page 439, left-hand column; table 1 ---	1-21
P,X	DEVANE: "Differential Pharmacology of Newer Antidepressants" THE JOURNAL OF CLINICAL PSYCHIATRY, vol. 59, no. S20, 1998, pages 85-93, XP002111619 page 88, right-hand column; table 3 -----	1,4-6, 11,12,19

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/06523

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-10
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

A compound cannot be sufficiently described by its mechanism of action or its pharmacological profile. A complete search can therefore not be made for "inhibitors" (claim 3).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/US 99/06523

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0687472 A	20-12-1995	AU 685510 B	22-01-1998
		AU 7742194 A	04-01-1996
		CA 2134038 A,C	17-12-1995
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